"CORRELATION BETWEEN CLINICAL ACTIVITY, ENDOSCOPIC SEVERITY & LABORATORY PARAMETERS IN ULCERATIVE COLITIS"

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CERTIFICATE

This is to certify that this dissertation entitled **"Correlation between clinical activity, endoscopic severity & lab parameters in ulcerative colitis"** submitted by **DR. R.Poppy Rejoice** to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032 in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by her under my direct supervision and guidance.

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CONTENTS

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the bowel, characterized by multiple relapses & remission ,which leads to significant morbidity and health care cost and is also challenging to the treating gastroenterologist.

All chronic diarrhoea and rectal bleeding during the year 1960 s were diagnosed as amoebic colitis or infective diarrhoea (1). Ulcerative colitis in India was first reported by Tandon and Chuttani et al (2). Various studies from India as well as from south India cites the increasing trends in ulcerative colitis (3).

UC affects the mucosal layer of the colon and produces multiple ulcerations, diffuse inflammation and desquamation of the colonic epithelium. The etiology of UC is unknown; however, genetic, immunologic, and environmental factors has a role in the pathogenesis of UC. The disease had a bimodal distribution. Both young adults & elderly individuals are at risk for developing this disorder.

The clinical presentations in UC varies , in severity, extent of disease, presence of extraintestinal manifestations & response to therapy.

It was found that 9% have severe, 71% have moderate & 20% of patients with mild disease activity at the time of presentation.

Diagnosis of UC is based on clinical, endoscopic and histo pathological findings. Mucosal assessment by colonoscopy is the best option in the diagnosis of ulcerative colitis . Newer diagnostic tools like chromoendoscopy ,NBI ,EUS have a definite role in the management of UC (4).

Severity of the disease is determined by assessing clinical symptoms, elevation in ESR or CRP & by fecal calprotectin. Dysplasia, colorectal malignancy, fulminant colitis were some of the feared complications of UC.

Response to therapy varies from patient to patient. Treatment is to prevent complications and to provide a better quality of life. Mucosal healing is the goal of therapy since it is associated with a decrease in colectomy rates and other complications like dysplasia and decrease in the incidence of relapse and use of corticosteroids.

The pattern of mucosal healing varies with different drugs used in UC. Various studies provides insight into the value of achieving mucosal healing (5).

Until recently, limited data from India is available about mucosal healing with various drugs in the management of UC. However, with the recent development of Multi-Matrix System (MMX) mesalamine, there are mucosal healing data from trials in UC (6).

Therefore the present study has been undertaken to asses the correlation of clinical disease activity with that of endoscopic activity in UC.

REVIEW OF LITERATURE

DR. Samuel Wilks first described Ulcerative colitis as idiopathic colitis and found that this disease is different from bacillary dysentery (7). In India UC was first reported by Tandon and Chuttani et al.

EPIDEMIOLOGY

UC is one of the most prevalent gastrointestinal diseases (8). The prevalence of UC ranges from 37 - 246 /100,000 persons (9). It is a common disease in most of the industrialized countries in the world. The highest incidence is reported from Scandinavia and Scotland and then from England and North America (10). It was thought to be uncommon in the developing countries but there is an increasing incidence & prevalence of UC in Hispanics and Asians & they are more likely to have UC than Chrons disease (11). UC has a bimodal age distributation, primarily in the third decade & again in the 7^{th} decade. Breast feeding, smoking and appendisectomy appears to have a protective role against UC (12,13).

INDIAN SCENARIO

A recent study from Indian sub continent found that the incidence of UC was 6.02/100000 / yr & a prevalence of 44.3/100000

population (14). Another prevalence study from Singapore revealed that the prevalence of UC was three times higher in Indians when compared with that of the Chinese (15) .In another report from UK in migrant South Asian group ,a higher prevalence of UC was noted in this group than in the Europeans(16).

PATHOPHYSIOLOGY

The interaction of genetic, environmental and immune factors play a role in the development of UC. Genetic factors were well demonstrated in twin studies. Genome-wide association studies showed that IL23R, HLA-DR1 & major histocompatibility complex (MHC) class II were associated with UC (17,18). Failure in the immune tolerance leads to dysfunction of epithelial barrier function & activate immune system to secrete various cytokines and chemokines resulting in inflammation.

Environmental factors like mycobacterial infection, dysbiosis (19) of intestinal microflora, diet like wheat, maize, cow milk were postulated to contribute to UC. Breast feeding, cigarette smoking and appendisectomy are strong negative predictors of UC.

Humoral and cellular immunity has a role in the pathogenesis of UC. Immune dysregulation is the likely factor.60 - 85% 0f UC patients have auto antibodies.

Psychogenic factors also has a role in the pathogenesis of UC.

PATHOLOGY

The disease starts from rectum and extends proximally with involvement of the mucosa in a continous and symmetrical manner but transmural involvement is rare. This feature differentiates UC from crohns disease. But in patients treated with enemas rectal sparing is seen. Periappendiceal involvement is another finding in UC.

DISTRIBUTION

In UC, inflammation begins above the anorectum and extends above in a diffuse manner. When inflammation is restricted to

The rectum	-	proctitis
From rectum to splenic flexure	-	left-sided colitis
Beyond the splenic flexure	-	extensive colitis
The entire colon	-	pancolitis.

MACROSCOPY

In mild disease the mucosa becomes hyperaemic. Edema and granularity are other features. When it becomes severe, it progress to hemorrhagic lesions with ulcers which increase in size & involve the lamina propria. Recurrent, relapses results in epithelial regeneration & leads to pseudopolyps . In chronic disease, mucosa become atrophy & have no specific feature .It is characterised by shortening & narrowing of the colon & also results in acute dilatation of the colon.

MICROSCOPY

In early stage of the disease edema, congestion ,acute inflammatory cell infiltration occurs. Cryptitis, crypt abscesses, goblet cell mucin depletion, mucopus are other features of UC. In chronic disease distortion of architecture of the crypt occurs , atrophy of crypts, increase in the space between crypts, irregular epithelial mucosa, basal aggregates of lymphoid cells & an infiltration of chronic inflammatory cells are seen. The severity of inflammation in histology will not correlate well with clinical activity in UC. (20)

THE DISTINCTION OF UC FROM CROHNS DISEASE

Inflammatory change in the terminal ileum (‘‘backwash ileitis’’), involvement of the ileum or proximal gastrointestinal tract distinguishes UC from Crohn’s disease. The inflammation in ulcerative colitis is continuous and mucosal-based, rarely extending beyond the most superficial layers of the submucosa. The inflammation in Crohn’s disease is almost always patchy, and importantly, it is transmural and aggregated. The aggregate may be lymphoid follicles, or in a minority of cases, it is granulomatous.

NATURAL HISTORY

UC is characterized by periods of remission and relapse. A population-based cohort study revealed that , at the time of presentation, 9% had severe disease, 71% & 20% had moderate and mild disease respectively. When they were followed at 3 to 7 years after initial diagnosis, they found that 25% were in remission, continuous disease activity was seen in 18% and intermittent relapses in 57%. At 25 years of follow-up, 90% had an intermittent course (21). The annual risk of relapse after remission for 1 year was estimated to be 20%.

CLINICAL PRESENTATION

Depends upon the anatomic location and severity of disease the clinical symptoms varies. Rectal bleeding is the commonest finding & may be massive, or associated with expulsion of mucopus. Diarrhoea is related to decreased rectal compliance. Tenesmus, urgency are other features. Constipation & vague pain abdomen can also occur. Patients can have constitutional symptoms, like fever, fatigability, joint pain, and loss of weight.

Proctitis is characterised by the presence of inflammation confined to the distal 15 cms of rectum .It is most commonly seen, and usually the mildest form of ulcerative colitis; constituting about 25% to 30% of cases .Patients with proctitis have bleeding per rectum, urgency, and sometimes constipation, because of late transit of fecal matter in the proximal colon. Other features like fever and other constitutional symptoms are uncommon.

Procto sigmoiditis and left sided colitis, accounts for about fourty percent of UC cases. Patients can have either constipation or diarrhea associated with tenesmus, and bleeding per rectum. In due course. It can progress proximally or retract to the distal colon.

Left sided colitis is characterised by inflammation upto the splenic flexure.

Extensive colitis and pancolitis have inflammation in the transverse colon and right colon. Patients presents with loose stools with bleeding per rectum, urgency and tenesmus. Abdominal pain may be localized or diffuse.

Toxic megacolon is the severe form of UC, characterised by inflammation involving the superficial mucosa and also into the submucosa & muscule layers. Fever, cramps, distention and rebound tenderness are other features.

EXTRAINTESTINAL MANIFESTATIONS

The commonest extraintestinal finding in IBD is arthritis. Involvement of the skin, eyes, mouth, joints & liver can occur. It can occur even prior, during or after exacerbations of intestinal disease (22). Peripheral arthropathy, cutaneous lesion & eye involvement were associated with severity of the disease.

DIAGNOSIS

Clinical findings, blood ,stool analysis & endoscopy in combination helps in the diagnosis of IBD and also to differentiate

ulcerative colitis from crohns disease as well as to exclude other diseases. Colonoscopy can define the distribution, severity, and disease activity and also to evaluate the response to therapy ,to determine the course of medical and surgical management. Multiple biopsies are taken, at least two from the terminal ileum, cecum, ascending, transverse descending and sigmoid colon, and also from the rectum even if the mucosa appears normal. In long standing disease colonoscopy plays an integral part in dysplasia and colorectal cancer surveillance (23).

Narrow band imaging (NBI), chromoendoscopy can be used to improve the yield from mucosal biopsies (24). Even then in 4% to 6% of IBD, it is difficult to differentiate UC and CD and it is termed as IBD-unclassified (IBDU) (25).

ASSESSMENT OF DISEASE EXTENT AND SEVERITY

Multiple clinical and endoscopic scoring methods are there to classify the severity of UC. The simplest clinical scoring system, is based on stool frequency, presence of fever, tachycardia, anemia, & elevated ESR(26).

Truelove and Witts Classification of the Severity of UC

Mild
<4 stools/day, with or without only small amounts of blood No fever No tachycardia Mild anemia ESR < 30 mm/hr
Moderate
Intermediate between mild & severe
Severe
>6 stools/day, with blood Fever > 37.5 C Heart rate > 90 beats/min Anemia with Hb level < 75% of normal ESR > 30 mm/hr

Other scoring systems were the Baron score, Mayo score, Powell-Tuck, Rachmilewitz endoscopic index, and the UC Disease Activity Index (27-29). Most of the scoring system are similar in their description of inactive, mild, moderate & severe UC.

ENDOSCOPIC ASSESMENT OF DISEASE ACTIVITY IN UC

Endoscopic Assessment	
0	Normal
1	vascular pattern is lost
2	Granularity, non friable
3	Friable on touch
4	Spontaneous bleeding & ulceration

SEROLOGICAL MARKERS

Perinuclear antineutrophil antibody (pANCA) is positive in 60-70% patients with UC. Combination of positive pANCA & negative anti–Saccharomyces cerevisiae antibody (ASCA) had a sensitivity, specificity and positive predicitive value of 57%, 97% & 92.5% respectievely. Elevated ESR, CRP also indicates severe disease.

DIFFERENTIAL DIAGNOSIS

A lot of inflammatory & non inflammatory conditions can mimic UC. They are Cronhs colitis, Infective colitis, Ischemic colitis, Amoebic colitis, Microscopic colitis and Pseudomembranous colitis.

WHAT IS MUCOSAL HEALING

In UC, IBD task force defined mucosal healing as the absence of friable mucosa, blood or erosions & absence of ulcers in all visualized sites of colonic mucosa (30). This is the endpoint for assessing disease activity. A population-based cohort study from Norway revealed that the presence of healing of mucosa 1 year following the diagnosis was significantly associated with a reduced need for colectomy at 5 years and reduced need for corticosteroids.

TREATMENT

The goals of treatment are control of symptoms, induction of remission, healing of endoscopic lesions, and prevention of complications.

Current management of UC has 3 main approaches: lifestyle modifications, medical therapy, and surgery. In mild to moderate disease

5-aminosalicylates (5-ASA) is still considered to be the first-line of treatment for induction & maintenance of remission (31). Oral aminosalicylates are useful in both proximal & distal colitis. Topical agents are effective in distal colitis. 40% and 80% clinical response is seen with sulfasalazine or its alternate forms in mild-to-moderate ulcerative colitis. The response rate varies between clinical trials due to different patient groups & end-point in the response.

In moderate to severe disease & in those who have no response for first-line 5-ASA therapy, corticosteroids are used for induction. Oral corticosteroids are not recommended for maintaining remission in ulcerative colitis. With severe disease, IV corticosteroid is indicated. Lack of improvement in 7 to 10 days is defined as failure of medical therapy and is an indication for proctocolectomy (32).

Immunomodulators consist of thiopurine derivatives such as 6-mercaptopurine and azathioprine and methotrexate and cyclosporine.

They are used in steroid-dependent or in 5-ASA refractory UC. Cyclosporine is used in the treatment of severe, steroid-refractory UC patients who face impending colectomy.

BIOLOGICALS

Infliximab (Remicade) is a chimeric, tumor necrosis factor monoclonal antibody, approved by the FDA both for induction & maintenance of remission in severe disease. It is also indicated for the treatment of extraintestinal manifestations of IBD, including ankylosing spondylitis, pyoderma gangrenosum, and chronic uveitis (33). Patients are started treatment with an induction dose of five mg/kg intravenously at weeks zero, two, and six, then with maintenance infusions every 8 weeks. In partial responders, the dose can be raised to 10 mg/kg.

The efficacy of infliximab therapy in adults with UC was evaluated in the, double-blind, placebo-controlled RCT termed Active Ulcerative Colitis Trial 1 and 2 (ACT-1 and ACT-2) (34). Thus, treatment with infliximab is helpful in inducing response in patients with moderate-to-severe active UC and also maintains a response if treatment is continued at 8-week intervals after the induction period.

Adaluzimab is not approved for treatment of UC. However, open-label trials showed ADA is useful in induction & maintenance of remission in active UC in patients intolerant or refractory to standard therapy (35). In the recent ULTRA 2 study ADA was used in assessing

the efficacy of induction and maintenance of clinical remission in patients with moderate-to-severe UC.

Natalizumab is a humanized IgG_4 monoclonal antibody against lymphocyte adhesion molecules, α_4 integrins currently is approved for treating patients with Crohn's disease as a second line therapy; but its use in UC is now under evaluation.

Other new anti-adhesion molecule is MLN-02 (*LDP-02*), a humanized IgG_1 monoclonal antibody to $\alpha_4\beta_7$ integrin. In a phase 2 trial, 2 infusions of 0.5 mg/kg of MNL-02 given at 29 days apart were effective in attaining response at 6 weeks in moderately active UC.

SURGICAL MANAGEMENT

Approximately 25% to 35% of UC patients will require surgery for their disease. Indications are severe, fulminant, steroid-refractory disease, the presence of dysplasia on targeted or random biopsies, and the detection of colorectal cancer. The most common surgical intervention for UC patients is total proctocolectomy with either an end-ileostomy or with an ileal-pouch anal anastomosis (IPAA).

HEALTH MAINTANANCE

Osteopenia and osteoporosis are common problems in UC patients. The risk of osteopenia and osteoporosis in UC is estimated to have a prevalence as high as 70% (36). Patients with evidence of osteopenia should be checked for vitamin D deficiency and treated accordingly. Patients with osteoporosis should begin treatment with a bisphosphonate.

Nutritional deficiency like iron deficiency due to blood loss and chronic inflammation; iron studies should be checked and repleted. Folate and vitamin B12 levels are also important to assess, especially in patients with anemia. Sulfasalazine impairs folate absorption, thus patients on this drug should receive daily folate supplementation.

Colorectal cancer screening is a part of management in UC. Major gastroenterological societies recommend regular annual surveillance with colonoscopy in those who had pancolonic UC for 8 or more years and 12 to 15 years of left sided colitis after initial diagnosis. 5-ASAs may have a role in decreasing the risk of CRC in UC, but further studies are needed.

A sizable percentage of UC patients have not been immunized against vaccine-preventable infections. IBD patients should routinely be

vaccinated for the following if they are not yet immune: hepatitis A, hepatitis B, influenza, tetanus, streptococcal pneumonia (Pneumococcus), diphtheria, pertussis, and varicella. Meningococcus and human papilloma virus vaccines should be administered to target populations (adolescents and young women, respectively). It is important to administer vaccinations prior to the administration of immunomodulators, anti-TNF therapy, or steroids.

Fertility is decreased for both men and women with IBD. In men, ongoing therapy with immunomodulators (MTX, 6-MP) fertility rate is decreased.

WHICH IS THE BETTER WAY TO DETERMINE RESPONSE TO THERAPY IN UC: SYMPTOMS OR ENDOSCOPIC ASSESSMENT?

In clinical practice, the response to disease activity in UC is determined by assessing clinical symptoms such as the presence or absence of blood, the number of stools per day, and the presence or absence of evidence of systemic toxicity. In addition, to this other means such as elevation in the ESR or CRP can be useful in assessing the severity of UC.

Mucosal healing is the best ultimate goal, because it is associated with long period of remission, steroid sparing and decreases colectomy rates. It also decreases dysplasia and colorectal malignancy.

AIM AND OBJECTIVES OF THE STUDY

1. To evaluate whether the clinlcal disease severity in ulcerative colitis and lab parameters reflect the degree of endoscopic activity.

2. To asses whether endoscopic findings during remission predicts the future clinical disease pattern.

MATERIALS AND METHODS

This is a pospective study conducted in the Department of digestive health and diseases, Govt. peripheral hospital, Annanagar, Kilpauk Medical College, Chennai from April 2012-february 2013.

INCLUSION CRITERIA:

Patients with a clinical diagnosis of ulcerative colitis , who underwent colonoscopic examination and had histological confirmation of ulcerative colitis were included.

EXCLUSION CRITERIA:

Infectious enterocolitis

Colorectal cancer

Crohn's disease

Indeterminate colitis

Pregnancy

Children

History of colorectal operation

NSAID or intake of aspirin (≥2 tablets/week).

First the study protocol was designed and our institution ethical committee approved the design of the study. Then the patients taken for this study were explained about the whole study and an informed consent was obtained.

The patients who came to our out patient department during the study period with a diagnosis of ulcerative colitis were included. All the particulars of the patients were obtained as per proforma attached here with . Patients were interviewed about their demographic details first. Then detailed history about clinical presentation , duration of illness, past history, personal and family history, environmental and psychological factors prior to the onset of disease were asked. A thorough clinical examination was done. Complete hemogram, basic blood chemistry, liver function test CRP were done as per proforma. The patients was also looked for the presence of extra intestinal manifestations. Disease severity was assesed using Truelove and Witts classification and they were stratified into mild, moderate and severe disease respectively.

Simultaneous Colonoscopic examination was performed . All the patients undergoing colonoscopy were prepared with PEGLEC as per our routine hospital protocol. Patients were instructed to be on liquid diet 24 hours prior to colonoscopy. One packet of PEGLEC powder mixed with

two liters of plain water was asked to drink in split doses, half in the previous day evening and another half in the morning. Patients were allowed to take only clean liquid following that.

Colonoscopy was done in the morning. Colonoscopy was done with PENTAX video colonoscope . Endoscopic assessment and grading was done for all patients who underwent colonoscopy (Baren et al). Biopies were taken as required and sent to our pathologist for tissue diagnosis.

Diagnosis of UC was made by combination of clinical, endoscopic appearance and histopathological examination. Only histopathologically confirmed cases from our hospital during the study period were taken for this study.

Baseline clinical severity, laboratory parameters and endoscopic grading were recorded for all these patients. These patients were treated as per the standard treatment protocol . These patients were in follow up and looked for clinical response.

Clinical remission was reflected by a normal frequency of bowel movements and no bleeding per rectum. Once the patient was in clinical remission and compliant with therapy ,they were all subjected to a repeat

colonoscopic examination at 3 and 6 months respectievely and the treatment response was assesed based on mucosal healing (Baron *et al* : 0-normal, 1-granular oedematous mucosa with absence of vascular pattern, 2-bleeds on touch, 3-spontaneous bleed). Lab parameters were also done during this time. Analysis was done to find the correlation between clinical severity and endoscopic activity of the disease at remission.

STATISTICAL ANALYSIS

While studying the relation between test results, clinical severity and endoscopic grading ,the chi square test or Fishers exact test was used when appropriate, and a multivariate analysis was performed using a logistic regression analysis. Significance was assigned to any probability value of less than 0.05.

The statistical software package SPSS for windows version (SPSS Inc, Chicago III) was used to analyse the data. Mean and standard deviations were used to summarize data for continous variables whereas percentages were used for categorical variables.

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RESULTS

In this study 14428 patients attended our OPD as new cases. Out of which 158 had bleeding per rectum and diarrhea. 101 patients had history and clinical features suggestive of Inflammatory bowel disease were included. All patients who gave consent under went laboratory examination and colonoscopic examination. 48 patients were excluded due to various reasons like

Not given concent for colonoscopy	2
Histology Tuberculosis	3
Histology non specific colitis	22
Cronhs disease	2
Infective colitis	2
Ischemic colitis	1
Not willing for follow up colonoscopy	12
Poor compliance & not in remission	4

DEMOGRAPHIC DETAILS

Table 1 Demographic profile

AGE	Numbers	%
<20 yrs	1	2
21-30 yrs	16	30
31-40 yrs	15	27
41-50 yrs	11	21
51-60 yrs	8	14
>60 yrs	3	6

Among the 53 patients 30 were male and 23 patients were female. Sex ratio was 1.3:1. Age ranges from 16 to 64 years. 36 year was the mean age . Peak age at which disease onset was noted was in the third decade. All the patients were from the geographical location around north Tamilnadu. 95% of them belongs to low socioeconomic group.

DURATION OF SYMPTOMS

Table 2 Duration of symptoms

DURATION	NUMBER	%
<6 MONTHS	39	73.6
6 MONTHS-2 YRS	10	18.9
2-5 YRS	4	7.5

The average period of symptoms prior coming to the hospital ranges from 15 days to 5 years. 73.6% had disease duration less than 6 months.

RISK FACTORS

Using the questionnaire the risk factors were analyzed. One patient had family history of IBD. In this study 6% were previous smokers. 4% had history of NSAID intake. None of them had previous history of appendisectomy. None was on oral contraceptive pills.

CLINICAL PRESENTATION

The commonest clinical presentation was diarrhea, but nocturnal symptom was present in 32%. Rectal bleeding was present in 69.8% of cases. 9.4% had fever. Pain abdomen , tenesmus, urgency were other features.

CLINICAL ASSESMENT OF SEVERITY-TRUELOVE AND WITTS CLASSIFICATION

TABLE 3:CLINICAL SEVERITY OF DISEASE

TRUELOVE AND WITTS	NUMBER	%
MILD	31	58.5
MODERATE	12	22.6
SEVERE	10	18.9

According to Truelove and Witts classification ,mild disease was commonly encounted in this study (58.5%). 22.6% had moderate disease. Severe disease was present in 18.9%.

LABORATORY FINDINGS

TABLE 4:BASELINE LAB PARAMETERS

	N	Minimum	Maximum	Mean	Std. Deviation
Albumin (gm/dl)	53	2.2	4.2	3.30	1.194
Platelet count (lakhs)	53	1.5	4.6	2.515	1.2922
ESR (mm)	53	7	98	31.77	23.352
HB (gm %)	53	6.0	14.3	10.443	1.7455
CRP (mg/dl)	53	2	98	13.42	18.496
TC (cmm)	53	1200	12900	8057.4	2324.598

CORRELATION OF DISEASE ACTIVITY WITH CLINICAL & LABORATORY PARAMETER

Nocturnal diarrhoe (P=.01) and fever (P=.03) had a positive correlation with clinical severe disease activity.CRP is a marker of active disease.(P=.000).

TABLE 5:CLINICAL ACTIVITY & LAB PARAMETERS

VARIABLES	Mild	Moderate	Severe	P value
TC	21/31	3/12	3/10	.065
HB	20/31	10/12	6/10	.070
ESR	7/31	4/12	4/10	.061
CRP	2/31	7/12	8/10	**.000**
ALBUMIN	7/31	3/12	1/12	.072
PLATLETS	4/31	1/12	3/10	.082
NOCTURNAL DIARRHOEA	5/31	5/12	7/10	**.01**
RECTAL BLEEDING	31/31	4/12	2/10	.062
FEVER	0/31	0/12	5/10	**.03**

ENDOSCOPIC DISTRIBUTATION OF DISEASE

At initial presentation ,the endoscopic pattern was

Proctitis	35.8%
Proctosigmoiditis	26.4%
Left sided colitis	13.2%
Extensive colitis	5.6%
Pancolitis	18.9%

Proctitis was the commonest presentation in this study. None of the patients had acute fulminant colitis.

ENDOSCOPIC DISTRIBUTATION AND CORRELATION OF CLINICAL & LAB PARAMETERS

Tenesmus and urgency were associated with proctitis and proctosigmoiditis. Presence of fever had a positive correlation with pancolitis. Laboratory variables when correlated with disease distribution, CRP correlated well with proximal distribution of disease CRP (P=.001)

CLINICAL SEVERITY AND ENDOSCOPIC DISTRIBUTION OF DISEASE

Distal colon is involved if the patient had a mild clinical activity. Extensive colitis and pancolitis were associated with severe disease activity.

TABLE 6:CLINICAL & ENDOSCOPIC CORRELATION

Trueiove & witts	**Proctitis**	**Procto Sigmoiditis**	**Left sided colitis**	**Extensive colitis**	**Pancolitis**
Mild	**17**	**14**	1	0	0
Moderate	2	0	5	0	3
Severe	0	0	1	**3**	**7**
Total	19	14	7	3	10

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	63.692(a)	8	.000
Likelihood Ratio	64.304	8	.000
Linear-by-Linear Association	37.457	1	.000
N of Valid Cases	53		

EXTRAINTESTINAL MANIFESTATIONS

15 % had extra intestinal manifestation in this study. Vascular thrombosis, axial & peripheral arthropathy and uveitis were the manifestations. None of them had neither cutaneous lesion nor primary sclerosing cholangitis.

TABLE 7: EXTRAINTESTINAL MANIFESTATIONS

SYSTEM INVOLVED	PRESENT	%
RHEUMATOLOGY	3	6
OPTHAL	2	4
CUTANEOUS	0	0
HEPATOBILIARY	0	0
VASCULAR	3	6

TREATMENT GIVEN TO THE PATIENT

36 patients(67.9%) were treated with sulphasalazine,14 (26.4%) were treated with sulphasalazine and prednisolone and 3(5.6%) with azathioprine and prednisolone respectievely. Biologicals were not used. All had clinical remission in this study.

CLINICAL VS ENDOSCOPIC REMISSION FOLLOWING TREATMENT

36 patients with mild to moderate disease were treated with sulphasalazine in the dose of 4 gms per day. Colonoscopy was done at three months and six month, while the patients were continuously taking

sulphasalazine therapy. During this time all of them were in clinical remission. The endoscopic findings at 3 & 6 months were compared with the baseline colonoscopic findings.

SULPHASALAZINE THERAPY AND MUCOSAL HEALING

No mucosal healing was noted in 80.5% and 70.5% at 3 and 6 months. A partial mucosal response was noted in19.5% and 25% respectievely at three and six months. **Sulphasalazine therapy was not associated with a complete mucosal healing in this study.**

TABLE :8 ENDOSCOPIC RESPONSE & SULPHASALAZINE THERAPY

DURATION	PARTIAL	COMPLETE	TOTAL RESPONSE	NO RESPONSE
3 MONTHS	7	**0**	7/36 19.5%	29/36 **80.5%**
6 MONTHS	9	**0**	9/36 25%	27/36 **75%**

MUCOSAL HEALING IN SULPHASALAZINE AND PREDNISOLONE GROUP

Fourteen were treated with sulphasalazine, four gms per day and oral prednisolone 40 mgs / day for 4 - 6 weeks, followed by decreasing the dose of prednisolone. Colonoscopy at three months , response was noted in 21.4%.All of them had a partial response only.

They were followed at 6 months both clinically and endoscopically. All of them were in clinical remission but 42.9% had an endoscopic response. Also 40% had a distal shift in distribution of disease.

TABLE :9 ENDOSCOPIC RESPONSE IN SULPHASALAZINE WITH PREDNISOLONE

DURATION	PARTIAL	COMPLETE	TOTAL RESPONSE		NO RESPONSE
3 months	3	0	3/14	**21.4%**	11/14
6 months	5	1	5/14	**42.9%**	8/14

ENDOSCOPIC RESPONSE IN AZATHIOPRINE & PREDNISOLONE GROUP

6 of them was initially in this group .Because of the intolerance to drug, 3 of them moved to the other group. In this group, complete, partial and nil response was observed in 33% each respectievely, both at three and six months.

ROLE OF LABORATORY PARAMETERS DURING THE FOLLOW UP PERIOD

All the lab parameters were also repeated during the follow up period. But no correlation was noted between ESR, CRP with the clinical disease activity during the third and sixth months. During which time, even though all the patients were in clinical remission. they haven't attained endoscopic healing.

T-Test

TABLE :10 Paired Samples Correlations

		N	Correlation	Sig.
Pair 1	CRP 1& CRP 2	53	.694	.060
Pair 2	CRP 1& CRP3	53	.445	.017

COMPLICATIONS

Skin rash 2

Anemia 4

Obesity 3

Exacerbation of symptoms following endoscopy were seen in 4 patients.

No major adverse reactions were encountered during the study period.

DISCUSSION

Ulcerative colitis is a common disease in most of the industrialized countries in the world, but it was thought to be uncommon in the developing countries (37). The highest incidence is reported from Scandinavia and Scotland and then by England and North America (38). In the West, the incidence and prevalence of UC is 8–14 per 100,000 and 120 -200 per100,000 persons, respectively (39).

Limited community studies were available from India. One community study from Punjab reveals the incidence of UC was 6.02/100000 per year and a prevalence rate of 44.3/100000 population.(40) but several hospital incidence rates were available from India and it was 12/10,000 by Sood et al 1999.

But in this study the hospital incidence of UC was 36/10000. An increasing trend was noted The temporal association of the increasing incidence rates is related to the change in westernisation of lifestyles, change in diet as well as in the environment caused by industrialization and urbanization (41).

Age ranges from 16 -64 years and the mean age was 36 years in this study. The maximum number of patients were in the third decade.

Following were the various studies on UC, from India

Author		**Mean (yrs)**	**Range (yrs)**
Sood et al	Ludhiana	31.7	14-65
Khosla et al	Rohtak	24.4 (M) 38.0 (F)	
Kapur P et al	Delhi		13-65
Kochhar et al	PGI		13-78
Chuttani et al	MAMC	31.5 (M), 25.3 (F)	9-56

Patients in India present mostly in 3rd and 4th decade and failed to show a bimodal age pattern (42). But in the West a bimodal distribution was noted characterized by a small late surge in the elderly, between 60 and 70 years.(43).

Males were affected slightly more than females, the ratio being 1.3:1. Another study by Tandon et al ,Delhi ,the sex ratio was 1.5:1. Most studies from West did not showed any difference among gender in the occurrence of UC. The male-to-female ratio of about 1 : 1 was found in all age groups.(44).

In this study, the average duration of symptoms prior coming to the hospital ranges from 15 days to 5 years. 73.6% had disease duration less than 6 months**.** Similar result was observed in a North Indian study and the mean duration of symptoms before coming to hospital entry was 2.7 years.

Association of IBD among family, occurs in first-degree relatives The relative risk of UC in a sibling was estimated to be around 7% and 17% based on western studies .Here also 1 patient (1.8%) had family history of IBD.

CLINICAL ASSESMENT OF SEVERITY-TRUELOVE AND WITTS CLASSIFICATION

On the basis of Truelove and Witts classification majority had mild disease (58.5%) at presentation. Moderate and severe disease were noted in 22.6% & 18.9% respectievely . A recent review report says that ulcerative colitis in India runs a mild course (45). The disease course reported in Indian immigrants in England and Durban was mild to moderate on clinical presentation (46). In the West there was a variance in the severity of disease reported in epidemiological studies and hospital based studies.

ENDOSCOPIC DISEASE ACTIVITY

At initial presentation 35.8% had proctitis and 26.4% had proctosigmoiditis. Distal disease was commonly noted in this study. Left sided colitis and extensive colitis were observed in 13.2% & 5.7% respectievely. Pancolitis was present in 18.9%. In a study from India half of the patients had left sided colitis (47.5%), proctosigmoiditis in 25% and pancolitis in 27.5%.

In one of the latest reviews from the West (47), 46% had proctosigmoiditis, 17% left sided colitis and 37% had pancolitis. According to a prospective, Norwegian study,(48) at initial presentation, proctitis was present in 1/3 rd of patients, another one-third had left sided colitis, in the remaining third there was proximal extension beyond the splenic flexure. Pancolitis was seen in 25% of the patients.

The distribution of the disease varies according to age, ethnicity and risk factors. A recent publication from Japan described that mild colitis and proctitis were significantly larger in patients who had onset of disease at older than 60 years, relatively to those who experienced onset at younger than 30 years ($P<.016$).(49).

CLINICAL PRESENTATION & ENCOSCOPIC DISEASE ACTIVITY

Diarrhoea and rectal bleeding were the commonest clinical presentation. Nocturnal diarrhea and fever had a positive correlation with the endoscopic severity of the disease. They had either extensive colitis or pancolitis. Kato and colleagues confirmed that severe clinical activity was seen more commonly in patients who had severe disease activity in the proximal colon compared with the rectum or sigmoid (50).

In this study, rectal bleeding and urgency were associated with distal colonoscopic lesion. Similar result was seen in another study from Tokyo (51).

LAB PARAMETERS & SEVERITY OF DISEASE

In this study patients with elevated CRP had either pancolitis or extensive colitis. It had a positive correlation with the severity of the disease. Similar result was seen in another study from Rochester.(52) In another Japanese study ,CRP elevation reflects the activity of proximal lesions.

ENDOSCOPIC ASSESSMENT OF RESPONSE TO TREATMENT

Sulfasalazine is a 5-ASA compound , used as first line therapy for the induction of remission in patients with mild to moderate UC. In this study, sulphasalazine therapy in mild to moderate disease had 100% clinical remission ,but not associated with a significant endoscopic response. No mucosal healing was seen in 80.5% and 75% at 3 and 6 months. Only a partial mucosal response was noted in19.5% and 25% respectievely at three and six months. Sulphasalazine therapy was not associated with a complete mucosal healing in this study.

In another study, sulfasalazine ,3 to 6 g/day induces remission in 39% to 62% with mild to moderate UC. A dose-dependent response was reported when it was used for induction in active UC.(43). In the ASCEND I &II trials, mesalamine at 2.4 & 4.8 gm per day in mild disease had similar efficacy, but in moderate active disease a higher dose(4,8 gm) was more effective to induce mucosal healing. This dose of mesalamine is comparable to 12 grams of sulphasalszine.

Recent studies have concluded that improved release formulations of 5 ASA & more aggressive dosing schedules were needed for inducing remission in UC. Dosages of mesalamine of less than 2.0 g/d are ineffective for inducing remission.

The poor response to sulphasalazine in this study can be attributed to the lower dose 4 grams per day, used in this study.

In case of sulphasalazine and prednisolone combination therapy, mucosal healing was seen in 21.4% & 42.9 % respectievely at 3 and 6 months in this study. The long-term remission rate in patients on glucocorticoids for severe UC is reported as approximately 50% (43).

Another report says, with corticosteroids, 54% achieved complete remission, 30% partial response, and 16% no response over first 30 days. (53).

In AZA and prednisolone group, mucosal healing was found in 66 %.No response was seen in 33%. One randomised controlled trial showed that azathioprine along with glucocorticoids had a response rate of 79% at one month. A varying result was given by another trial, the response rate was 53% at six months.

Rutgeerts et al ,in his study Infliximab produces mucosal healing in about 50% of patients at 30 weeks.

Kohn et al ,in a small series reported that 77% clinical response was seen after a single infliximab infusion of 5 mg/kg, & 80% of the responders were in clinical remission after a period of 2 years.

ROLE OF CRP AND MUCOSAL HEALING

In this study, CRP that was done subsequently at 3 & 6 months while the patients were in clinical remission doesn't correlate with the clinical activity. This might be because of the presence of endoscopic disease activity. Solern et al,in his study elevated CRP is a marker of endoscopic activity.(52)

COMPLICATIONS

No major complications were encounted during this study. Recent data from IBSEN study with 10-year follow-up also did not observe a significant increased risk of death in patients with UC.(55)

Mild exacerbation of clinical symptoms were noted following colonoscopy in 4 patients. Recent colonoscopy is associated with a flare in UC.(56)

CONCLUSION

1. This study fails to show a bimodal age distribution in UC.

2. On the basis of Truelove and Witts classification majority had a mild disease.

3. Proctitis was the commonest colonoscopic finding in this study.

4. Mild clinical disease was associated with distal colitis and severe disease was found to have either extensive or pancolitis.

5. Nocturnal diarrhea and fever were observed more commonly in patients who had maximum disease activity in the proximal colon compared with the rectum or sigmoid.

6. CRP elevation reflects the activity of proximal lesions .

7. In patients with mild to moderate disease none of the patients had a complete mucosal healing response with sulphasalazine therapy at 3 and 6 months respectievely .Sulphasalazine 4 grams may be a suboptimal dose.

8. Elevated CRP during the follow up period ,while the patient is in clinical remission indicates the absence of mucosal healing. This can be used as an indirect marker to predict future response.

9. Full colonoscopy is particularly important in the initial mapping of disease extent and severity as well as to investigate any discrepancy between clinical symptoms and endoscopic appearance.

10. Mucosal healing as assessed by endoscopy is a useful tool for evaluating and guiding response to therapy in patients with IBD.

11. Mucosal healing is an admirable goal that we should strive to achieve in each of our patient on a regular basis.

LIMITATIONS OF THIS STUDY

1. Dose of sulphasalazine is probably short of therapeutic range in moderate UC.

2. Sample size were small in steroid and azathioprine group.

3. Biologicals were not used.

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ANNEXURE – A

PROFORMA

NAME AGE SEX:

DDHD NO: DIAGNOSIS: DURATION:

EPIDEMIOLOGY	Drug
Place	Skin/Eye problem
Per capita income	CAD
COMPLAINTS	**PAST HISTORY**
Pain abdomen	DM
Loose stools	HTN
Nocturnal symptoms	Surgery
Blood in stools	**FAMILY HISTORY**
Fever	IBD
Fatigue, tiredness	**PERSONAL HISTORY**
Weight loss	Smoker
Jaundice	Alcahol abuse
Joint pain	Tabacco

GENERAL EXAMINATION	INVESTIGATIONS
BMI	HB
Temperature	TC
Pulse	DC
BP	ESR
Pallor	PLATELET
Skin lesions	ALBUMIN
Jaundice	RFT
Eyes	CRP
Oral cavity	STOOL
Joints	**TRUELOVE &WITTS**
Peripheral vessels	Mild
ABDOMEN	Moderate
RECTAL	**Severe**

	Baseline(1)	**3 months (2)**	**6 months (3)**
COLONOSCOPY			
ESR			
CRP			
HB			
TC/DC			
PLATELET			

ANNEXURE – B

MASTER CHART

No	Age	sex	dura-tion	diar-rhoea	rectal bleed	fever	platelet	ESR 1	HB1	CRP 1	true luv	colon 1	colon 2	TC	HB 2	ESR2	CRP2	ESR 3	CRP 3	colon 3	extra	treatment
1	54	m	2	4	2	0	1.5	7	11.7	6	S1	P1	P1	6500	11.9	8	7	7	5	P1	nil	S
2	60	f	3	3	3	0	2.3	10	11	2	S1	P2	P2	5342	10.8	12	8	10	4	P1	nil	S
3	30	f	3	4	1	0	1.8	11	10.8	8	S1	P1	P1	7800	11	11	8	8	6	P1	nil	S
4	63	f	0.5	6	2	0	1.9	30	8.7	11	S2	P2	P2	9100	8.5	10	5	16	17	P2	nil	S
5	47	m	2	4	4	0	2.4	120	6.6	13	S1	P2	P2	7600	9.5	37	7	11	3	P2	nil	S
6	25	f	3	4	4	0	4.8	60	9.3	24	S1	L2	L2	8240	10	28	11	12	6	L2	DVT	S
7	60	f	3	4	3	0	1.9	20	12	5	S1	PS1	PS1	7600	11.8	12	6	21	3	PS1	nil	S
8	30	m	1	5	4	0	1.6	23	11	7	S1	PS2	PS1	7333	11.7	10	3	11	5	PS1	nil	S
9	42	m	2	15	12	0	1.9	97	11.8	13	S3	PA3	PA1	8900	12.8	34	7	22	8	PS3	nil	SP
10	38	m	12	4	3	0	2.6	12	14.3	3	S1	P2	P2	7600	11.8	7	5	21	4	P2	nil	S
11	38	f	48	4	4	0	2.8	13	12.5	8	S1	P1	P1	8110	12.9	10	4	22	11	P1	nil	S
12	64	m	0.25	4	2	0	1.7	11	13.2	4	S1	PS2	PS2	6500	13	8	6	6	5	PS2	nil	S
13	22	m	24	10	10	0	2.8	28	10.3	98	S3	PA3	L3	9100	12	16	17	11	5	PS2	nil	SP
14	42	f	4	4	3	0	3	21	11	5	S1	P1	P1	7600	11.8	11	3	8	3	P1	nil	S
15	54	f	3	4	3	0	1.9	12	12.9	6	S1	PS2	PS2	9300	12	12	6	5	5	PS2	nil	S
16	31	m	3	4	4	0	3.1	39	10	5	S2	PA2	E3	8000	11.3	21	3	6	5	P2	nil	SP
17	16	m	4	12	2	0	2.1	11	14	3	S2	P2	P2	6200	13.8	11	5	6	6	P2	nil	S
19	22	m	6	4	3	0	2.3	52	8	5	S1	PS1	PS1	6720	9	22	8	11	12	PS1	nil	S
10	22	m	3	0	3	0	2.7	12	10	8	S1	P1	P1	5880	11.2	21	4	9	9	P1	nil	S
20	38	m	24	5	3	0	2.6	23	11	4	S1	PS2	PS2	7600	12	22	11	14	4	PS2	nil	S
21	42	m	1	14	12	1	2.2	43	10.7	76	S3	PA2	E2	8400	11.8	6	5	11	6	E1	nil	SP
22	36	m	3	4	3	0	2	17	11.3	5	S1	P2	P2	6500	11.8	11	5	21	5	P2	nil	S
23	54	m	2	8	8	1	3.6	30	10.4	55	S3	E2	E1	4800	11	8	3	9	8	E1	nil	SP
24	30	m	6	7	6	0	1.8	34	12	13	S2	PA2	PA2	9320	11	5	5	18	6	PA2	nil	SP
25	35	m	0.5	4	3	0	1.6	12	11.4	7	S1	P2	P2	7600	10.6	6	5	11	3	P2	nil	S
26	20	f	6	4	3	0	1.5	21	12	5	S1	P2	P2	5700	11	6	6	10	5	P2	nil	S
27	57	f	2	10	9	0	1.8	54	7.9	17	S3	PA2	PA2	9800	8.5	11	12	37	7	PA2	nil	SP
28	28	f	36	15	12	1	1.9	43	6	43	S3	PA3	PA3	11900	9.8	9	9	28	11	PS1	nil	SP

No	Age	sex	dura-tion	diar-rhoea	rectal bleed	fever	platelet	ESR 1	HB1	CRP 1	true luv	colon 1	colon 2	TC	HB 2	ESR2	CRP2	ESR 3	CRP 3	colon 3	extra	treatment
29	52	f	18	0	3	0	2	13	11	4	S1	PS3	PS3	7690	11	14	4	12	6	PS3	nil	S
30	55	m	12	4	4	0	2.8	17	10.7	4	S1	PS2	PS2	3560	11.9	11	6	10	3	PS2	nil	S
31	60	f	3	3	2	0	3	10	12	6	S1	PS2	PS2	6700	11	21	5	34	7	PS2	nil	S
32	33	m	12	0	2	0	1.8	23	8.6	16	S1	P2	P2	12000	9.7	9	8	7	5	P2	nil	SP
33	41	f	6	7	6	0	4.5	83	9.6	23	S3	E2	E2	12400	10.6	18	6	10	4	E2	nil	S
34	28	m	3	4	4	0	1.6	12	11,8	5	S1	P2	P2	1200	11.7	11	3	8	6	P2	nil	S
35	45	m	12	0	4	0	1.9	23	12	7	S1	PS2	PS2	7800	11.9	8	3	16	17	PS2	nil	S
36	37	m	6	4	3	0	1.7	21	11	5	S1	P2	P2	6500	12	16	4	11	3	P2	nil	S
37	22	m	4	7	6	0	1.6	43	7.8	12	S2	L3	L3	9700	9.7	35	7	12	6	L3	E	S
38	32	f	24	4	4	0	3.6	23	9.8	8	S2	PS3	PS3	6890	10.7	12	5	21	3	PS3	nil	S
39	36	m	3	12	8	0	3.2	34	9.7	8	S2	L2	L2	6500	10.8	22	3	11	5	L2	nil	S
40	38	m	12	4	4	0	3.7	12	10	5	S1	P2	P2	8900	11	11	6	22	8	P2	nil	S
41	28	f	24	20	15	1	3.4	32	7.9	12	S3	E2	PS2	5800	9.6	19	7	21	4	PS2	nil	SP
42	45	f	7	0	3	0	2.3	40	12.3	6	S1	PS2	PS2	4560	12	11	4	22	11	PS2	nil	S
43	40	m	2	8	6	0	2.6	45	10.5	6	S2	PA3	P2	10700	11	12	7	6	5	P2	nil	AP
44	21	f	6	6	6	0	9.6	23	11	7	S2	L2	L2	9200	11	12	4	11	5	L2	DVT	S
45	41	f	4	7	4	0	1.8	82	9.2	10	S2	L3	PS	12700	10	40	7	8	3	P2	nil	AP
46	38	m	6	7	6	0	1.9	34	9.4	9	S2	L2	L2	8200	10.2	15	3	5	5	PS1	nil	SP
47	31	f	60	4	4	0	2.4	25	9.8	5	S1	PS3	PS3	10700	10	17	7	6	5	PS3	nil	S
48	28	f	3	15	12	0	4.9	23	9.7	12	S3	PA2	PS2	12900	11	21	7	6	6	E3	DVT	SP
49	25	m	12	15	6	1	1.8	64	7.3	54	S3	PA2	PA2	11700	8.9	34	10	11	12	PA2	R	AP
50	36	m	4	8	6	0	1.8	43	9.4	12	S2	L2	L2	8200	10	21	7	9	9	L2	nil	S
51	43	f	24	8	nil	0	1.9	40	12.4	5	S1	PS2	PS2	11200	11	21	3	14	4	PS2	nil	S
52	34	m	3	4	4	0	1.6	21	9.8	4	S1	P2	P2	7800	11	12	5	11	6	P2	nil	S
53	28	f	7	4	3	0	1.8	32	11	7	S1	P2	P2	8500	10.7	17	2	21	5	P2	nil	S

"CORRELATION BETWEEN CLINICAL ACTIVITY, ENDOSCOPIC SEVERITY & LABORATORY PARAMETERS IN ULCERATIVE COLITIS"

DISSERTATION SUBMITTED FOR

DM MEDICAL GASTROENTEROLOGY

BRANCH- IV

AUGUST 2013